Pathologic relationship of ulcer and carcinoma of the alimentary canal / Louis Blanchard Wilson and Byrd Charles Willis.

PATHOLOGIC RELATIONSHIP OF ULCER AND CARCINOMA OF THE ALIMENTARY CANAL.*

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INTRODUCTORY

Any line of investigation which promises assistance in combating the spread of cancer is worth while. For, discounting to the utmost government census figures everywhere, there yet remains the facts, first, that cancer is increasing materially in relation to the total number of deaths from all causes, and, second, that it is increasing materially in relation to the total number of living. Speaking broadly, it is probably increasing more rapidly than any other of our diseases. And this increase is greatest in the most prosperous nations and in the most prosperous classes within such nations. Further, it attacks individuals at their highest productive period. It attacks particularly the primary organs of perpetuation of the individual, i. e., the reproductive apparatus. In the male approximately two-thirds and in the female one-fourth of all cancers develop in the alimentary canal, while one-half of all cancers of the female are in the reproductive organs.

It seems to us that in our consuming interest in the initial excitant or ultimate cause of cancer, there is a possibility of our losing sight of the importance of the study of the tissue conditions of the affected individual. When the relationship of bacteria to infectious disease was first brought to the attention of the scientific world for a long time the specific germ was the chief object of study. Experience soon taught us, however, that in combating infectious diseases it is even more important

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that we familiarize ourselves with those conditions of the body by which nature combats disease. We are apt to forget that if we knew to-day the primary irritant in carcinoma as well as we know the leprosy bacillus we might still be almost as helpless as we now are in controlling the disease. We would still be under the necessity of investigating most carefully the anatomic and physiologic condition of the tissues which permit the primary excitant, whatever its nature, to become effective.

CLINICAL EVIDENCE

From the purely clinical standpoint, probably the most salient points which present themselves in relation to tissue susceptibility to carcinoma are the following:

1. Carcinomata of the reproductive organs in the female—one-half of all cancers in this sex—occur principally at the age when the reproductive organs have begun their regressive changes.

2. Carcinomata of the alimentary canal—two-thirds of all cancers in the male—follow in the great majority of cases chronic non-cancerous irritation.

ANATOMIC EVIDENCE

When once removed from the body, tumors of the alimentary canal are of relatively easy study, because of the comparatively simple anatomic relationships; the thin walls with well-defined laminæ and simple glands. The lips, mouth and anus are, of course, exceptions to this. When we examine carcinomata of the alimentary canal we find them in a great majority of cases developing on epithelial tissue which has been displaced either by ulcerative changes or by diverticula. An ulcer of the mucous membrane of the alimentary canal shows within its base usually only granulation tissue, all of the tubular glands having been destroyed. At the margin of the ulcer is an overhanging border consisting of hyperplastic mucosa. Where this hyperplastic area meets the eroded base is a ring in which are found islets of tubular epithelium which have been cut off from their connection with the outer world by bands of scar tissue.

The center of the ulcer, filled with granulation tissue, is almost always on a level with that of the normal base of the mucosa, within which is the ring containing segregated epithelium. The tendency of such islets of segregated epithelium is toward destruction by the cutting off of their blood-supply by scar tissue. In a careful study

of these cell inclusions, however, we frequently find that many of the islets instead of degenerating show more or less proliferation of their cells. This is evidenced by their apparently increased number in a cross-section, by their mitotic figures and their dividing nuclei. Such inclusions are of frequent occurrence around the borders of all ulcers of the stomach, duodenum, gall-bladder, appendix and large intestine. It is probable that the proliferation of the epithelium within such inclusions is frequently stopped by the cutting off of the blood-supply, and that degeneration results. When, however, we study many lesions of this type, particularly within the stomach, we find that certain groups of epithelium show not only proliferation of their cell contents, but that the proliferating cells are infiltrating the surrounding tissues; that this is a true passage of the epithelium into the previously formed scar tissue. That the picture is not due to the presence of remains of included epithelium which has been only partially cut off from its normal site there can be no doubt in the mind of one who studies the sections with proper care. The epithelial cells which are insinuating themselves between the bands of fibrous tissue are not old degenerating cells, but are cells which are proliferating, as is shown by their staining reactions and their dividing chromatin. It is noteworthy that this proliferation is usually most marked in the portion of the epithelium-bearing ring which is furthest removed from the center of the ulcer with its scant nutrition. More than 70 per cent of all of our cancers of the stomach give satisfactory gross and microscopic evidence of previous ulceration and isolation of epithelium, while the evidence is equally clear in our cancers of the gall bladder. We have seen at no point within the alimentary canal any evidence that surface irritation, however prolonged, has anything to do with providing conditions suitable for the development of carcinoma. It seems to be a *sine qua non* that the portions of epithelium shall be displaced from their normal relationship, and this does not occur where superficial irritation alone is concerned, but only in ulcers and diverticula.

The relationship of small diverticula of the alimentary canal to carcinoma has not been fully appreciated, partly because the presence of the diverticula themselves have been but recently called to our attention. When

Drs. Mayo, Giffin and Wilson placed on record our five cases of diverticulitis of the sigmoid three years ago. there were on record only eighteen previous cases. One of these presented a carcinoma of a diverticulum. The number of cases of diverticulitis has increased during the subsequent three years until there are now on record nearly one hundred cases. We have added five new ones to our list. In these five two are cases in which the operation was made primarily for well advanced carcinoma and diverticula were found in the base of the carcinoma. The epithelium within small diverticula is frequently quite as completely occluded from connection with the interior of the viscus as is that lying at the base of an ulcer of the stomach. Here, as in the isolated islets of epithelium within the stomach, the tendency of the segregated cells is to degeneration from reduced nutrition. They do, however, occasionally proliferate greatly and, as we have shown in three of our nine cases, they may also infiltrate and thus form carcinoma. When one goes over a number of cases of carcinoma of the sigmoid one is struck with the patch-like or ring-like character of all of the lesions, except those of the most advanced type. This is exactly the sort of tumor which one would expect to find developing on isolated epithelium within diverticula, and the two tumors whose origin, as we have demonstrated, has been on diverticula, are of exactly this type. In order to show the presence of diverticula in carcinomata of the sigmoid which have advanced to any extent, it is necessary to use the utmost care in examining the specimen while it is still fresh.

Sometimes with fresh specimens this can be done by very gently probing from the inner side of the tumor, or better still, by carefully slicing off the tumor from the serous surface and parallel thereto, and examining underneath each slice as it is removed. We are satisfied from our experience that many cases of carcinoma of the sigmoid and rectum have had their origin on diverticula which have been overlooked at operation, even when they were still undestroyed by the tumor.

In the last 5,000 appendices which have been removed at our clinic we have discovered twenty-two primary carcinomas. In reviewing these recently, Drs. MacCarty and McGrath have noted that all of these tumors have occurred in the tips of appendices which had been previously obliterated. This obliteration in all cases ex-

tended well proximal to the tumor, and showed the formation of scar tissue at some point proximal to the tip in greater quantities than in the tip itself. The glandular epithelium of the tip of the organ has been separated from the lumen of the caecum. Such epithelium is frequently found to show hyperplasia or adenomatous proliferation. In the twenty-two cases which we have found, however, there is much more than this, viz., an infiltration of the deeper layers of the appendix, resulting in unmistakable primary carcinoma.

In the tough fibrous stroma of the border of the lips it is difficult to make out mieroscopically any evidence of flat-cell inclusions. The lips of practically all adults have been so frequently subjected to traumatic scars, ulcers, etc., as the result of nutritional disturbances that it would seem probable that such inclusions of the epithelium are frequently present. Carcinomas of the lip, however, usually come to the clinic so late that all microscopic evidence of their previous benign ulceration has disappeared, though the clinical histories recite such evidence in an unmistakable manner.

Within the mouth the relationship of ulcerating leukoplakia to subsequent carcinoma is established on a very firm clinical basis, though here, as in carcinoma of the lip, the patients most frequently come to operation at a period when all microscopic evidence has been swallowed up in the advance of the secondary disease.

To summarize, then, the results of our studies, we may say that in the alimentary canal, whatever may be the essential irritant—micro-organisms, ferment or what not—the fact remains that in a very high percentage of the cases there is microscopic evidence backing up clinical evidence that the carcinomata have developed on epithelial cells which have been previously isolated from their normal surroundings, either by the formation of diverticula or by being cut off by scar tissue in ulcer bases. This statement has in it neither support nor contradiction for any hypothesis as to the character of the essential irritant in carcinoma. Just as we must have tissue cut off from sufficient blood-borne oxygen in a punctured wound in order to permit development of the tetanus bacillus, so it seems that in the alimentary canal we must have tissue which is cut off from its relationship with the outside world in order to have the development within it of whatever may be the essential irritant

of carcinoma. Whether this isolation of epithelium is a primary necessity for the formation of carcinomata throughout the body is another question. Certain it is that a similar condition exists in the female breast which is undergoing regression. Certain it is that similar conditions exist in the uterus, with its partially shed epithelium, with its frequent erosions, and with its regressing mucosa. Certain it is that a similar condition exists in the prostate as the result of inflammatory changes segregating islands of epithelium. Within the kidney true carcinomas are frequently associated with the ulcerated process secondary to nephrolithiasis, while the so-called "hypernephromata," on the other hand, are apparently the result of the proliferation of tissue which has failed to become connected embryologically with the portion of the tubular epithelium which is in direct relation with the renal pelvis. Indeed, as we look over the whole field of carcinomata we must agree with Adami that these tumors are the result of the development on either postnatally or prenatally displaced cells which exhibit a tendency to revert to the embryonic type.

The clinical bearing of all of this is in teaching the importance of the recognition and cure of those disease processes which, however benign in themselves, tend to isolate epithelium. There can be no question but that chronic ulcers of the mouth should be promptly cared for. Ulcers of the stomach should receive the most minute attention. The obliterating appendix, however innocent its look, should invariably be removed when found. Diverticula of any portion of the large intestine should be treated by complete removal rather than by a drainage of the abscesses which may be formed about their extremities. The greatest difficulty of course is in the early diagnosis, but that is without the province of this paper.

PATHOLOGIC MATERIAL STUDIED

167 cancers of lip.
46 cancers of mouth and tongue.
2 cancers of esophagus.
189 cancers of stomach.
15 cancers of gall-bladder.
22 cancers of appendix.
20 cancers of cecum.
42 cancers of remainder of colon.
67 cancers of rectum.

570

SUMMARY

Of the cases of cancer of lip 30 per cent. gave evidence of previous isolation of epithelium.

Of the cases of cancer of stomach 67 per cent. gave such evidence.

Of the cases of cancer of gall-bladder 33 per cent. gave such evidence.

Of the cases of cancer of appendix 100 per cent. gave such evidence.

Of the cases of cancer of cecum 10 per cent. gave such evidence.

Of the cases of cancer of colon 40 per cent. gave such evidence.

Of the cases of cancer of rectum 3 per cent. gave such evidence.

CONCLUSIONS

1. The relationship to cancer of simple chronic irritation of the unbroken free surface of the mucosa of the alimentary canal, as indicated by clinical data, is not readily demonstrable pathologically.

2. Scar tissue at the bases of ulcers, obliterations of the lumina of appendices, and diverticula segregate portions of mucous epithelium from the neighboring epithelium and from the lumen of the alimentary canal.

3. These portions of segregated mucous epithelium tend (a) to degenerate from pressure and diminished blood-supply, or (b) to proliferate and infiltrate the surrounding tissues, thus forming cancer.

4. These islands of segregated epithelium probably should be regarded as points of least resistance only, and requiring the presence of other factors for the production of carcinomata.

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